General

Guideline Title

Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health.

Bibliographic Source(s)

Mogayzel PJ Jr, Naureckas ET, Robinson KA, Mueller G, Hadjiliadis D, Hoag JB, Lubsch L, Hazle L, Sabadosa K, Marshall B, Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013 Apr 1;187(7):680-9. [90 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions of recommendation grade (A, B, C, D, or I), estimate of net benefit (Substantial, Moderate, Small, or Zero/Negative), and certainty of net benefit (High, Moderate, or Low) are provided at the end of the "Major Recommendations" field.

Summary of Recommendations Unchanged From Previous Guidelines

Treatment	Recommendation	Certainty of Net Benefit	Estimate of Net Benefit	Recommendation
Inhaled tobramycin—moderate to severe disease*	For individuals with cystic fibrosis (CF), 6 years of age and older, with moderate to severe lung disease and *Pseudomonas aeruginosa* persistently present in cultures of the airways, the CF Foundation strongly recommends the chronic use of inhaled tobramycin to improve lung function and quality of life, and reduce exacerbations.	High	Substantial	A
Inhaled tobramycin—mild disease*	For individuals with CF, 6 years of age and older, with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of inhaled tobramycin to reduce exacerbations.	Moderate	Moderate	B
Dornase alfa—	For individuals with CF, 6 years of age and older, with moderate to	High	Substantial	A

Treatment	Recommendation	Certainty of Net Benefit	Estimate of Net Benefit	Recommendation
moderate to severe disease*	severe lung disease, the CF Foundation strongly recommends the chronic use of dornase alfa to improve lung function, improve the quality of life, and reduce exacerbations.			
Dornase alfa—mild disease*	For individuals with CF, 6 years of age and older, with asymptomatic or mild lung disease, the CF Foundation recommends the chronic use of dornase alfa to improve lung function and reduce exacerbations.	High	Moderate	B
Inhaled hypertonic saline	For individuals with CF, 6 years of age and older, the CF Foundation recommends the chronic use of inhaled hypertonic saline to improve lung function and quality of life and reduce exacerbations.	Moderate	Moderate	B
Azithromycin with *P. aeruginosa*	For individuals with CF, 6 years of age and older, with *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of azithromycin to improve lung function and reduce exacerbations.	High	Moderate	B
Oral antistaphylococcal antibiotics, prophylactic use	For individuals with CF, the CF Foundation recommends against the prophylactic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations.	Moderate	Negative	D
Inhaled corticosteroids	For individuals with CF, 6 years of age and older, without asthma or allergic bronchopulmonary aspergillosis, the CF Foundation recommends against the routine use of inhaled corticosteroids to improve lung function or quality of life and reduce pulmonary exacerbations.	High	Zero	D
Oral corticosteroids	For individuals with CF, 6 years of age and older, without asthma or allergic bronchopulmonary aspergillosis, the CF Foundation recommends against the chronic use of oral corticosteroids to improve lung function, quality of life or reduce exacerbations.	High	Negative	D
Other inhaled antibiotics	For individuals with CF, 6 years of age and older, with *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of other inhaled antibiotics (i.e., carbenicillin, ceftazidime, colistin, gentamicin) to improve lung function and quality of life or reduce exacerbations.	Low	–	I
Oral antipseudomonal antibiotics	For individuals with CF, 6 years of age and older, with *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the routine use of chronic oral antipseudomonal antibiotics to improve lung function and quality of life or reduce exacerbations.	Low	–	I
Leukotriene modifiers	For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the routine chronic use of leukotriene modifiers to improve lung function and quality of life or reduce exacerbations.	Low	–	I
Inhaled or oral N-acetylcysteine, or inhaled glutathione	For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of inhaled or oral N-acetylcysteine or inhaled glutathione to improve lung function and quality of life or reduce exacerbations.	Low	–	I
Inhaled anticholinergics	For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of inhaled anticholinergic bronchodilators to improve lung function and quality of life or reduce exacerbations.	Low	–	I

Treatment	Recommendation	Certainty of Net Benefit	Estimate of Net Benefit	Recommendation

*Severity of lung disease is defined by forced expiratory volume in 1 second (FEV_1) % predicted as follows: normal, >90% predicted; mildly impaired, 70%–89% predicted; moderately impaired, 40%–69% predicted; and severely impaired, <40% predicted (Flume et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med* 2007;176:957–969).

New and Modified Recommendations

Treatment	Recommendation	Certainty of Net Benefit	Estimate of Net Benefit	Recommendation
Ivacaftor*	For individuals with CF, 6 years of age and older, with at least one G551D CF transmembrane conductance regulator (*CFTR*) mutation, the Pulmonary Clinical Practice Guidelines Committee strongly recommends the chronic use of ivacaftor to improve lung function and quality of life and reduce exacerbations.	High	Substantial	A
Inhaled aztreonam—moderate to severe disease†	For individuals with CF, 6 years of age and older, with moderate to severe lung disease and *Pseudomonas aeruginosa* persistently present in cultures of the airways, the CF Foundation strongly recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.	High	Substantial	A
Inhaled aztreonam—mild disease†	For individuals with CF, 6 years of age and older, with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.	Moderate	Moderate	B
Chronic use of ibuprofen (age <18 yr)	For individuals with CF, between 6 and 17 years of age, with an FEV_1 ≥60% predicted, the CF Foundation recommends the chronic use of oral ibuprofen, at a peak plasma concentration of 50–100 μg/ml, to slow the loss of lung function.	Moderate	Moderate	B
Chronic use of ibuprofen (age ≥18 yr)	For individuals with CF, 18 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of oral ibuprofen to slow the loss of lung function or reduce exacerbations.	Low	–	I
Azithromycin without *P. aeruginosa*	For individuals with CF, 6 years of age and older, without *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of azithromycin should be considered to reduce exacerbations.	Moderate	Small	C
Chronic inhaled β2-adrenergic receptor agonists	For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against chronic use of inhaled β2-adrenergic receptor agonists to improve lung function and quality of life or reduce exacerbations.	Low	–	I
Oral antistaphylococcal antibiotics, chronic use	For individuals with CF, 6 years of age and older, with *Staphylococcus aureus* persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations.	Low	–	I

*CF Foundation personnel did not participate in any activity related to ivacaftor.

†Severity of lung disease is defined by forced expiratory volume in 1 second (FEV_1) % predicted as follows: normal, >90% predicted; mildly

impaired, 70%–89% predicted; moderately impaired, 40%–69% predicted; and severely impaired, <40% predicted (Flume et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med* 2007;176:957–969).

Definitions:

U.S. Preventive Services Task Force Evidence Grading*

Certainty of Net Benefit	Magnitude of Net Benefit			
	Substantial	Moderate	Small	Zero/Negative
High	A	B	C	D
Moderate	B	B	C	D
Low	I (insufficient evidence)			

The overall strength of the evidence is based on the certainty of the magnitude of benefit defined as benefit minus harm.

Quality of the Evidence*

High. The available evidence includes consistent results from well designed, well conducted studies in representative populations. This conclusion is therefore unlikely to be strongly affected by the results of future studies.

Moderate. The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.

Low. The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; findings not generalizable; lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

Strength of Recommendation*

A. The committee strongly recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is substantial.

B. The committee recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.

C. The committee recommends that clinicians consider providing this therapy to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms there is likely to be only a small benefit from this service.

D. The committee recommends against the therapy. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. Clinicians should discourage the use of this service.

I. The committee concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

*Adapted from: U.S. Preventive Services Task Force Grade Definitions.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Cystic fibrosis

Guideline Category

Management

Treatment

Clinical Specialty

Family Practice

Infectious Diseases

Internal Medicine

Pediatrics

Pulmonary Medicine

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Physician Assistants

Physicians

Respiratory Care Practitioners

Guideline Objective(s)

- To provide guidance to clinicians in evaluating and selecting appropriate treatment for individuals with cystic fibrosis (CF)
- To provide up-to-date evidence of safety and efficacy of chronic treatments of CF lung disease, including the use of novel therapies that have not previously been included in CF pulmonary guidelines

Target Population

Children aged ≥6 years and adult patients with cystic fibrosis (CF)

Interventions and Practices Considered

1. Inhaled tobramycin
2. Dornase alfa
3. Inhaled hypertonic saline
4. Azithromycin
5. Ivacaftor
6. Inhaled aztreonam
7. Chronic use of ibuprofen in patients <18 years

Note: The following were considered and recommended against: prophylactic use of oral antistaphylococcal antibiotics, inhaled corticosteroids, chronic use of oral corticosteroids.

Note: The following had insufficient evidence to recommend for or against use: other inhaled antibiotics (carbenicillin, ceftazidime, colistin, gentamicin), oral antipseudomonal antibiotics, leukotriene modifiers, inhaled or oral N-acetylcysteine, or inhaled glutathione, inhaled anticholinergics, chronic use of ibuprofen in patients ≥18 years, chronic inhaled β_2-adrenergic agents, chronic use of oral antistaphylococcal antibiotics.

Major Outcomes Considered

- Pulmonary function (forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], forced expiratory flow [FEF] between 25% and 75% of FVC [$FEF_{25\%-75\%}$])
- Incidence of new infections
- Progression of lung disease
- Reduction in exacerbations
- Quality of life
- Adverse effects of medications

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A multidisciplinary committee composed of 17 members reviewed the 2007 guidelines and developed a series of questions related to chronic drug therapies for cystic fibrosis (CF). An evidence review was commissioned from The Johns Hopkins University, with systematic reviews completed for each question. New reviews were conducted for each question, as some questions were new or revised, new medications and indications were considered, and because a full systematic review was not completed for all questions in the development of the 2007 guidelines. The review was limited to parallel and cross-over randomized controlled trials (RCTs).

In January 2011, the evidence review team completed searches of PubMed, Excerpta Medica (EMBASE) database, and the Cochrane Central Register of Controlled Trials (CENTRAL). They combined controlled vocabulary terms and text words for cystic fibrosis and each therapy being reviewed to create comprehensive search strategies. Reviews and animal studies were excluded; however, no date or language restrictions were applied during the search. The evidence review team also conducted manual searching of reference lists of included or eligible articles and relevant review articles, and asked the members of the guideline committee to review the included and excluded studies.

The original search was completed in January 2011. An additional review question on ivacaftor was added in December 2011 and the databases were searched for ivacaftor-related articles in December 2011.

Number of Source Documents

The search identified a total of 6,898 unique citations, of which 57 were included in the 2007 guidelines (see Figure 1 in the original guideline document). The current guidelines are based on review of 137 articles describing 84 studies (see Table 2 in the original guideline document). Because some questions addressed in the current guidelines differ from those posed in the 2007 guidelines, 14 studies reviewed previously were not included in the current literature review.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

U.S. Preventive Services Task Force Evidence Grading*

Certainty of Net Benefit	Magnitude of Net Benefit			
	Substantial	Moderate	Small	Zero/Negative
High	A	B	C	D
Moderate	B	B	C	D
Low	I (insufficient evidence)			

The overall strength of the evidence is based on the certainty of the magnitude of benefit defined as benefit minus harm.

Quality of the Evidence

High. The available evidence includes consistent results from well designed, well conducted studies in representative populations. This conclusion is therefore unlikely to be strongly affected by the results of future studies.

Moderate. The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.

Low. The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; findings not generalizable; lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

*Adapted from: U.S. Preventive Services Task Force Grade Definitions.

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

A multidisciplinary committee composed of 17 members reviewed the 2007 guidelines and developed a series of questions related to chronic drug therapies for cystic fibrosis (CF). An evidence review was commissioned from The Johns Hopkins University, with systematic reviews completed for each question. New reviews were conducted for each question, as some questions were new or revised, new medications and indications were considered, and because a full systematic review was not completed for all questions in the development of the 2007 guidelines. The review was limited to parallel and cross-over randomized controlled trials (RCTs).

Detailed methods are contained in the online supplement (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Subcommittees were created to review the evidence summaries and draft recommendations for presentation to the entire committee. Final recommendations were graded using the U.S. Preventive Services Task Force scheme, which encompasses an estimate of net benefit and certainty of net benefit.

The current committee affirmed previous recommendations for several therapies. A comprehensive review of these recommendations can be found in the online supplement (see the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Strength of Recommendation*

A. The committee strongly recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is substantial.

B. The committee recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.

C. The committee recommends that clinicians consider providing this therapy to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms there is likely to be only a small benefit from this service.

D. The committee recommends against the therapy. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. Clinicians should discourage the use of this service.

I. The committee concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

*Adapted from: U.S. Preventive Services Task Force Grade Definitions.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

A draft of the guidelines was posted on a secure web site for comment from Cystic Fibrosis Center care teams (physicians and ancillary care providers) and was revised as appropriate.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is specifically stated for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Safe and effective use of medications for maintenance of lung health in patients with cystic fibrosis (CF)

Potential Harms

- There is concern that the chronic use of azithromycin in individuals with occult or active nontuberculous mycobacteria (NTM) infection could lead to resistance, and thus complicate NTM treatment. For this reason, the committee suggests that patients should be screened for NTM before initiating azithromycin, and reassessed periodically at 6- to 12-month intervals. In addition, this monotherapy should be withheld in those infected with NTM.
- The most common side effects of inhaled hypertonic saline are cough and bronchospasm, which are well tolerated, particularly if subjects are pretreated by an inhaled bronchodilator.
- Voice alteration was noted as the most common side effect of dornase alfa, occurring in up to 18% of patients.
- Recommendations for chronic use of medications are based on relatively short trials. The committee recognizes that many intervention trials, even those ideally designed, have a finite duration. It is likely that patients will use medications for years or even decades, and that side effects (or benefits) might arise after very long-term use that were not anticipated based on shorter studies. Thus, clinicians must continue to monitor individuals for possible unanticipated side effects of these therapies.

Qualifying Statements

Qualifying Statements

These updated guidelines are based on a systematic review of the published literature. However, any therapeutic decisions must be made individually for each patient. The guideline authors hope that these recommendations will help cystic fibrosis (CF) health care professionals, individuals with CF, and their families make informed health care decisions. It is anticipated that these recommendations will be revised as new information becomes available.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Identifying Information and Availability

Bibliographic Source(s)

Mogayzel PJ Jr, Naureckas ET, Robinson KA, Mueller G, Hadjiliadis D, Hoag JB, Lubsch L, Hazle L, Sabadosa K, Marshall B, Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013 Apr 1;187(7):680-9. [90 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Apr 1

Guideline Developer(s)

Cystic Fibrosis Foundation - Disease Specific Society

Source(s) of Funding

Supported by the Cystic Fibrosis Foundation

Guideline Committee

Pulmonary Clinical Practice Guidelines Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Members of the committee disclosed any potential conflicts of interest. If any perceived conflict was present, members did not participate in any discussions or decisions on recommendations regarding that therapy. Author disclosures are available on the American Journal of Respiratory and Critical Care Medicine Web site.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the American Journal of Respiratory and Critical Care Medicine Web site.

Availability of Companion Documents

The following are available:

- Mogayzel PJ Jr, Naureckas ET, Robinson KA, Mueller G, Hadjiliadis D, Hoag JB, Lubsch L, Hazle L, Sabadosa K, Marshall B, Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Online data supplement. Electronic copies: Available in Portable Document Format (PDF) from the American Journal of Respiratory and Critical Care Medicine Web site.

Patient Resources

The following are available:

- Chronic medications: guidelines for CF lung health. Web cast. 2013. Available from the Cystic Fibrosis (CF) Foundation Web site. Also available as a slide presentation from the CF Foundation Web site.
- Therapies for cystic fibrosis. Information for patients. 2012 Feb. Available from the CF Foundation Web site.

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NGC Status

This NGC summary was completed by ECRI Institute on July 3, 2013. The information was verified by the guideline developer on July 18, 2013.

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